REMARKS/ARGUMENTS

Applicants respectfully request reconsideration and allowance of this application in view of the amendments above and the following comments. Claims 1-9 were pending in this application. By this amendment, claims 1-5 and 7 have been amended. No new matter has been added. Accordingly, claims 1-9 are pending.

Objection to claim 7

In response, applicants have amended claim 7, which now reads in part, "time-of-flight." Applicants, therefore, respectfully request that the Examiner reconsider and withdraw this rejection.

Rejection of claims 1-9 under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 1-9 as indefinite. In response, applicants have amended the specific claims, which were rejected. In respect to the Examiner stating that claim 2 is confusing because it is unclear as to how the ligands can be separated again using a hollow-fiber module in lines 7-8, applicants have amended claim 2 to make it clearer. Applicants, however, also note that the separation of the ligand from the affinity molecule involves 1) dissociation of the ligand from the affinity molecule and 2) the actual separation (i.e. into different fractions) of both components. Applicants, therefore, respectfully request that the Examiner reconsider and withdraw these rejections.

Rejection of claims 1 and 5-9 as being obvious over Oosterkamp et al in view of Hsieh et al under 35 U.S.C. §103(a)

In response, applicants assert that one skilled in the art would not be motivated to combine the teachings of Oosterkamp et al with Hsieh et al for the reasons listed below. As the Examiner acknowledges, Oosterkamp et al fails to teach the on-line coupling of the effluent of the fractionation to a mass spectrometer. Hsieh et al simply describes a screening method using chromatography coupled with mass spectrometry. Hsieh's method, however, requires a dual run, first in the absence of a library of protein targets, and then with such library. This means that background compounds, especially the affinity proteins, cause severe background signals over a broad range in the mass spectrum, which are always present in this assay, which would limit the efficiency, selectivity and flexibility of the method considerably. Thus, one would not be motivated to combine the teaching of Oosterkamp et al with the teaching of Hsieh et al because of the fact that the methodology of Hsieh et al is hampered by severe background signals. (see page 3 of the specification starting at line 3) This problem is overcome by the present invention because the claimed invention does not require a dual run, first in the absence of a library of protein targets, and then with such library. In contrast, in the claimed invention, the on-line coupling of the effluent of a fractionation step and a mass spectrometer (MS) greatly enhances the performance of both techniques, which allows for high selectivity and a high sensitivity without being hampered by severe background signals. Applicants, therefore, respectfully request that the Examiner reconsider and withdraw this rejection.

Rejection of claim 2 as being obvious over Oosterkamp et al in view of Hsieh as applied to claim 1 and further in view of Jurinke et al and Lutz et al under 35 U.S.C. §103(a)

In response, applicants assert that there is no motivation to combine Oosterkamp et al et al in view of Hsieh et al for the reasons listed above. In addition, specifically with respect to claim 2, applicants state that this claim is distinguished over the combination of Oosterkamp et al. and Hsieh et al in that it requires the dissociation of the ligand-affinity molecule complex, followed by separation of ligand from affinity molecule using a hollow fibre module and directing the permeate with the ligand to the MS. It is the Examiner's opinion that it would be obvious to carry out the dissociation step in view of the teaching of Jurinko et al.

Jurinko et al does show that complexes of biotin can be dissociated, after which the sample, can be analyzed in an MS. However, there is no suggestion in Jurinko et al that would lead the skilled person to the idea that the dissociation would be suitable in an on-line method, which requires a relative fast reaction time, preferably under ambient conditions and preferably without a need to remove the ammonia (or other dissociation aid). Jurink et al relates to a batch method (off-line method) not to an on-line method. One skilled in the art would not contemplate using Jurinke's technique in an on-line method because in Jurinke et al, the dissociation should preferably be carried out at an elevated temperature (at least 40° C in particular about 60°C), under pressure or in a sealed reaction vessel (See column 7, lines 17-22). These conditions are typically off-line conditions instead of conditions for an on-line method.

Finally, applicants assert that one would have no motivation to combine the teaching of Lutz et al with the other references for the following reasons listed below. Lutz et al relates to a method wherein a hollow fibre module is used for separating free and bound label in an on-line liquid chromatography-immunochemical detection method. Such module is used because of the fact that the detector cannot distinguish between the free label signal and the bound label signal in the samples, due to the fact that the fluorescence of the label in free form and in bound form are essentially the same (see paragraph bridging page 181 and 182). In

accordance with the present invention, the lack of differences in detection signal (in Lutz, i.e. fluorescence) is not relevant at all. In contrast to the detection technique described in Lutz et al., mass spectrometry is suitable to detect the ligand also in the presence of the affinity molecule. Thus, the skilled person would have no reason to use the hollow fibre membrane as taught in Lutz et al. Instead, the hollow fiber module is used for a completely different reason. Applicants, therefore, respectfully request that the Examiner reconsider and withdraw this rejection.

Rejection of claims 3-4 as being obvious over Oosterkamp et al in view of Hsieh as applied to claim 1 and further in view of Lutz et al under 35 U.S.C. §103(a)

Applicants, assert that the references do not make the claimed invention obvious for all the reasons discussed above. Applicants, therefore, respectfully request that the Examiner reconsider and withdraw this rejection.

CONCLUSION

Based on the foregoing remarks it is believed that the claim is in condition for allowance. However, should any issue(s) of a minor nature remain, the Examiner is respectfully requested to telephone the undersigned at telephone number (212) 808-0700 so that the issue(s) might be promptly resolved.

CONDITIONAL PETITION FOR EXTENSION OF TIME

If any extension of time for this response is required, Applicants request that this be considered a petition therefore. Please charge the required fee to Deposit Account No. 14-1263.

ADDITIONAL FEES

Please charge any further insufficiency of fees, or credit any excess to Deposit Account No. 14-1263

Respectfully submitted,

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